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LETTERS TO THE EDITOR

Sex-based differences in pneumococcal serotype distribution in adults with pneumococcal meningitis

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We read with interest the study by Gounder et al., on the epidemiology of bacterial meningitis in the North American Arctic following the introduction of paediatric conjugate vaccines, which was published recently in this journal.[1] Widespread use of paediatric conjugate vaccines has changed the epidemiological landscape of bacterial meningitis; however, it remains a serious health problem worldwide.[2] In the Netherlands, there has been a significant decrease in the incidence of adult bacterial meningitis since their inclusion in childhood immunisation schedules, most sharply among *Streptococcus pneumoniae* capsular serotypes included in the seven-valent (PCV7) and ten-valent (PCV10) pneumococcal conjugate vaccines.[3] These were introduced in the Netherlands in 2006 and 2011, respectively; a 23-valent polysaccharide vaccine (PPV23) is also available and recommended for certain risk groups.[4] Similarly to what Gounder and colleagues reported, *S. pneumoniae* is currently the leading cause of bacterial meningitis in the Dutch population.[3] As pneumococcal vaccines target only a limited set of the over 90 known serotypes,[5] emergence of non-conjugate vaccine type (NVT) disease remains a concern.[6]

Pneumococcal serotypes have been associated with differences in invasiveness potential and outcome,[4] making knowledge of factors affecting serotype distribution important. A patient's sex is a key determinant of infectious diseases, influencing susceptibility to illness and response to vaccination, while social and behavioural factors may also play a role.[7] Data regarding sex-based differences in pneumococcal serotype distribution, however, are limited,[8—10] and the impact of patient sex on serotype distribution in pneumococcal meningitis remains unclear. To investigate this, we analysed serotype distribution and post-vaccination incidence trends in adult men and women with community-acquired pneumococcal meningitis in a prospective nationwide cohort study.

We included all patients with pneumococcal meningitis, identified through the Netherlands Reference Laboratory for Bacterial Meningitis between March 2006 and June 2014, for whom capsular serotype was available. All participants or their legally authorized representatives provided informed consent. Pneumococcal meningitis was defined as a positive cerebrospinal fluid culture for

Table 1 Capsular pneumococcal serotypes from 447 men and 481 women with pneumococcal meningitis.

Serotype	Men — no. (%)	Women — no. (%)	p-Value
7F	54 (12)	56 (12)	0.82
3	59 (13)	47 (10)	0.10
8	43 (10)	35 (7)	0.19
22F	27 (6)	41 (9)	0.15
23F	21 (5)	23 (5)	1.00
19A	17 (4)	23 (5)	0.47
19F	15 (3)	19 (4)	0.64
10A	12 (3)	18 (4)	0.37
23B	15 (3)	15 (3)	0.82
4	13 (3)	15 (3)	0.86
12F	11 (2)	16 (3)	0.44
6B	11 (2)	14 (3)	0.68
1	8 (2)	15 (3)	0.20
14	8 (2)	15 (3)	0.20
18C	9 (2)	14 (3)	0.39
9N	8 (2)	13 (3)	0.35
11A	11 (2)	9 (2)	0.53
23A	10 (2)	10 (2)	0.86
28 other serotypes[a]	95 (21)	83 (17)	—
PCV7 types[b]	89 (20)	104 (22)	0.54
PCV10 types[c]	152 (34)	177 (37)	0.40
PPV23 types[d]	362 (81)	401 (83)	0.42
Total[e]	447	481	

Individual serotypes are presented in descending order of frequency. Abbreviations: PCV7, heptavalent conjugate vaccine; PCV10, 10-valent conjugate vaccine; PPV23, 23-valent polysaccharide vaccine.

[a] Other serotypes were as follows: 6A in eight males and ten females; 24F in seven male and nine females patients; 33F in nine men and eight women; 9V in 12 men and four women; 15B in four males and 11 females; 6C in seven male and five female patients; 16F in four men and six women; 35F in seven males and three females; 15A and 17F in five male and three female patients each; 28 in three males and three females; 31 in three men and two women; 15C in four males and two females; 20 in four males; 37 in four females; 18B in one male and three females; 5 in one male and two females; 34 and 35B both in two males and one female; 22A in two males; 10B, 13, 25A, 28F and 7B in one male each; 27, 24B and 7A in one female each.
[b] 4, 6B, 9V, 14, 18C, 19F and 23F.
[c] 1, 5 and 7F + PCV7 types.
[d] 2, 3, 9N, 10A, 11A, 12F, 15B, 17F, 19A 20, 22F and 33F + PCV10 types.
[e] Percentages may not add up to 100% due to rounding.

S. pneumoniae, and isolates were serotyped by Quellung reaction using specific antisera. Individual serotypes were grouped into vaccine types (i.e. those included in PCV7, PCV10 and PPV23) and NVT for analyses and compared between sexes using the Chi-Square or Fisher exact test (as appropriate), with Bonferroni correction for multiple testing. Incidence rates in men and women were calculated as the number of cases per 100,000 male or female population>16 years-old, respectively, per epidemiological year from July 2007 onward, as due to pending ethical approval in several centres this was the first year in which all Dutch hospitals participated in the study. Incidence rate ratios (IRR) and 95% confidence intervals (CI) were used to assess differences in incidence rates between men and women. Analyses were performed using IBM SPSS Statistics software (version 22.0), with two-tailed p-values below 0.05 considered statistically significant. Detailed methods of the MeninGene Study have been described previously.[3]

We identified 997 episodes of pneumococcal meningitis. Serotype was available in 928 (93%), of which 447 (48%) were male, and 46 distinct capsular types were identified (Table 1). Serotypes 3, 7F and 8, in that order, were the most commonly found in men, while 7F, 3 and 22F were the most frequent in women. After correcting for multiple testing, we found no differences between sexes in serotype
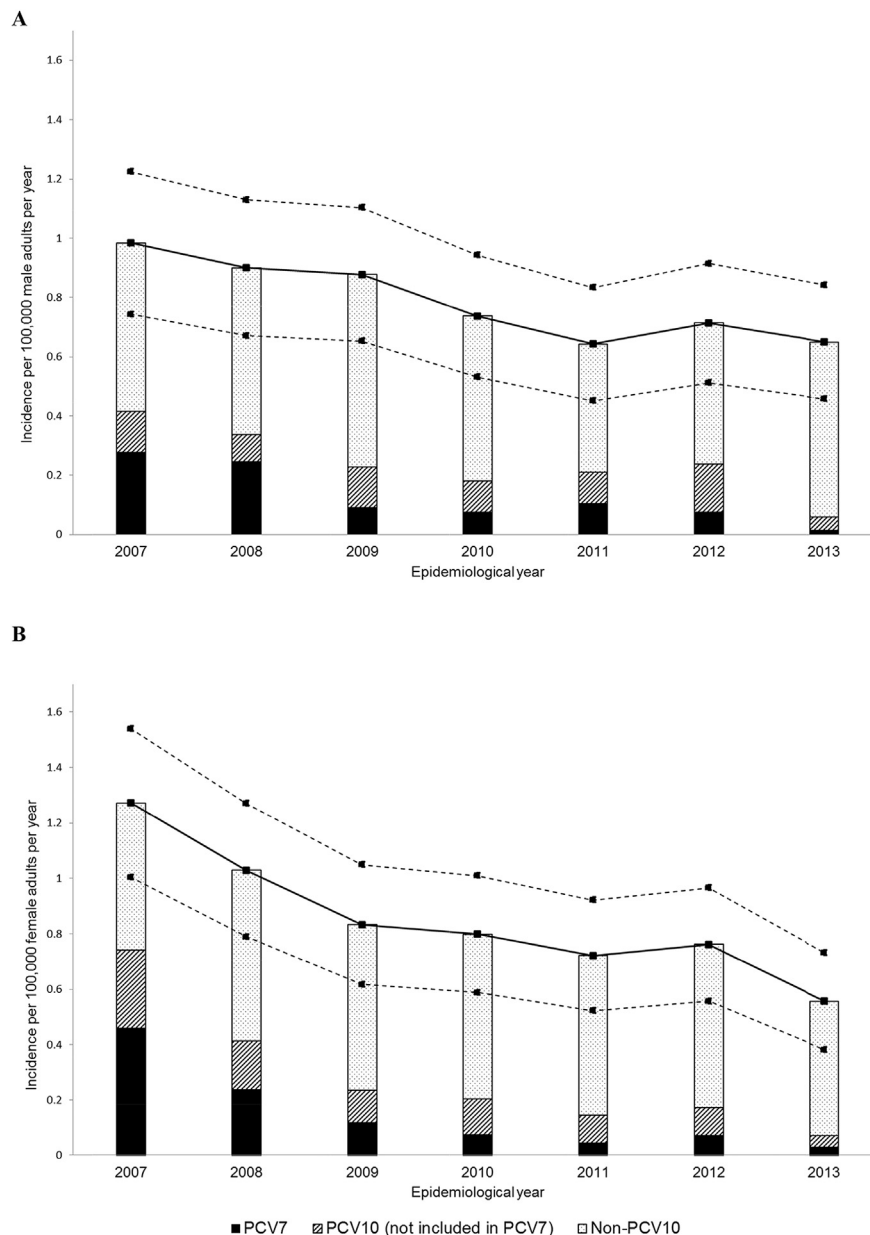

Figure 1 Total incidence of pneumococcal meningitis (solid line) with 95% confidence intervals (dotted lines) and incidence due to serotypes included in the PCV7 and PCV10 conjugate vaccines (bars) in men **(A)** and women **(B)** from 2007 to 2013. Due to pending ethical approval in several, not all patients could be included in the first months of the study, and therefore only cases from July 2007 onward were considered.

distribution, neither individually nor using serotype 7F as a reference (data not shown). We also found no differences between men and women in the proportion of episodes due to serotypes included in the PCV7, PCV10 or PPV23 vaccines.

Overall incidence of pneumococcal meningitis was 0.78/100,000 male and 0.85/100,000 female patients, with an IRR of 0.92 (95% CI 0.80−1.06). There was a marked decrease over the study period (Fig. 1), mainly driven by a reduction in the incidence of PCV7 serotypes in both sexes (from 0.37 in 2007 to 0.02 in 2013). Incidence of disease caused by PPV23-exclusive serotypes remained largely unchanged throughout the study period (from 0.41 in 2007 to 0.36 in 2013), with no difference between sexes. There was no absolute increase in the incidence of non-PCV10 types in either sex, although the proportion of cases caused by these types did rise, from 58% (37 of 64 cases) in 2007 to 91% (40 of 44 cases) in 2013 in men ($p < 0.001$) and 42% (36 of 86 cases) in 2007 to 87% (34 of 39 cases) in 2013 in women ($p < 0.001$).

In the Netherlands, coverage rates for conjugate vaccines in infants are around 95%, while adults are not routinely vaccinated.[4] As a result, sex-based differences in response to pneumococcal vaccination are unlikely to have influenced our results, as evidenced by the relative stability of disease caused by serotypes exclusive to the PPV23 during the study period. These findings are, therefore, best explained as a result of herd protection.

Parents are thought to often acquire pneumococci from their children, who are the primary community reservoir, and increased NVT carriage rates have been reported in parents of PCV7-vaccinated children.[10] In many societies, women are more active in childcare than men, which could favour acquisition of pneumococci, specifically NVT. However, although the female to male ratio in pneumococcal meningitis in our cohort was slightly higher when compared with non-pneumococcal cases, this was not statistically significant,[3] and there was no female preference for NVT disease.

We also found no significant sex-based differences in the distribution of individual serotypes. Literature on this topic is scarce, and studies have yielded varying results. Rodríguez et al., reported serotype 8 (not included in pneumococcal vaccines) to be more common in men, and 1 and 7F (both included in the PCV10) in women with invasive pneumococcal disease (IPD),[9] while van Mens and colleagues found increased serotype 1 IPD prevalence in young women[10]; a pre-vaccination study by Scott et al., described a female preference for serogroup 14 and 23 IPD.[8] It is possible these findings are the result of chance, natural fluctuation in serotypes, differences in methodology or publication bias. Furthermore, none of these studies specifically investigated meningitis, and potentially the influence of sex on serotype distribution may differ between meningitis and other types of IPD.

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Conflicts of interest

None.

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Simplification to a dual regimen with darunavir/ritonavir plus lamivudine or emtricitabine in virologically-suppressed HIV-infected patients

Dear Editor,

In this Journal, Buteel and colleagues explored the emergence of drug resistant HIV variants at virological failure (VF) of 3-drugs combinations (HAART) containing efavirenz, tenofovir and lamivudine or emtricitabine.[1] Recently, strategies of treatment switch to a dual therapy with atazanavir/ritonavir or lopinavir/ritonavir plus lamivudine in virologically-suppressed HIV-infected patients have shown promising results with low risk of virological failure and emergence of resistance.[2–4] However, few data are available for the darunavir/ritonavir + lamivudine or emtricitabine combination.[5]

We performed a multicenter, retrospective, observational study including patients on HAART, with HIV-RNA < 50 copies/mL and CD4 > 200 cells/μL switching during routine clinical practice to darunavir/ritonavir 800/100 mg plus lamivudine 300 mg or emtricitabine 200 mg once daily for intolerance to nucleoside reverse transcriptase inhibitors (NRTI) or to prevent NRTI toxicity. We excluded patients with positive HBsAg, pregnancy or genotypic resistance to darunavir or lamivudine/emtricitabine. All patients provided informed consent to be included in observational studies, approved by the institutional Ethics Committees.

Patients were followed from darunavir/ritonavir + lamivudine or emtricitabine initiation (baseline) to treatment discontinuation/switch (TD, defined as any modification or discontinuation of the dual regimen) or to the last available visit.

The primary endpoint was to estimate the time to TD and to explore its predictors using Kaplan–Meier curves and Cox regression models. Secondary endpoints included the evaluation of time to VF (defined as HIV-RNA > 50 copies/mL in two consecutive determinations or >1000 copies/mL in a single determination) and of CD4, lipid parameters and renal function evolution over time.

A total of 194 patients were included [145 (76.1%) males, median age 49 years (interquartile range, IQR 40–55), 33 (17%) HCV-coinfected, 45 (23.2%) with previous AIDS-defining events, median CD4 nadir 223 cells/μL (IQR 94–324), median baseline CD4 626 cells/μL (IQR 482–786), median time with HIV-RNA < 50 copies/mL 41 months (IQR 21–75)]. Previous HAART regimens were protease inhibitor (PI)-, non-nucleoside reverse transcriptase inhibitor (NNRTI)- or integrase inhibitor (InSTI)-based in 125 (64.4%), 33 (17%) or 25 (12.9%) patients, respectively. The NRTI backbone included tenofovir in 78.4% (Supplementary Table 1).

At baseline, 186 (96%) and 8 (4%) patients simplified treatment to darunavir/ritonavir + lamivudine and darunavir/ritonavir + emtricitabine, respectively. The median follow-up after baseline was 8.8 months (IQR 4.8–19.8).

VF was observed in 7 (3.6%) patients with an incidence of 3.7 per 100 person years of follow-up (PYFU). Five of them (2.6%) switched treatment with subsequent virological control. The remaining 2 patients (1.0%) remained on dual therapy with spontaneous virological re-suppression. Genotyping testing at VF, available for 1/7 patients, did not demonstrate any resistance mutation.

Overall, TD occurred in 44 (22.7%) patients with an incidence of 23 per 100 PYFU. Main reasons of TD were: adverse events [n = 22 (11.3%), incidence 11.5 per 100 PYFU], simplification to PI monotherapy or single tablet regimens [n = 6 (3.1%), incidence 3.1 per 100 PYFU], virological failure [n = 5 (2.6%), incidence 2.6 per 100 PYFU], inadequate adherence [n = 4 (2.1%), incidence 2.1 per 100 PYFU]. Main adverse events leading to TD were dyslipidemia (n = 10, 5.2%) and gastrointestinal intolerance (n = 6, 3.1%).

The estimated probabilities of VF and TD were 5.6% and 18.7% at 12 months, respectively (Fig. 1a and b). A higher probability of TD was observed for patients switching from InSTI-based (40.3%) when compared to PI-based (13.9%) and NNRTI-based regimens (12.6%) (p = 0.004); this difference was mainly driven by TD for adverse events (Fig. 1c and d). Exploring predictors of TD, pre-switch InSTI-based regimens [adjusted hazard ratio (aHR) 2.63, 95%